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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/786,034	04/23/2001	Gerardo Castillo	PROTEO.P07CI3	4033

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EXAMINER	
DELACROIX MUIRHEI, CYBILLE	
ART UNIT	**PAPER NUMBER**
1614	

DATE MAILED: 11/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/786,034	CASTILLO ET AL.	
	Examiner	Art Unit	
	Cybille Delacroix-Muirheid	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 March 2004 and 15 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-3, 6, 8-11, 13, 16-17, 19-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *20-25* is/are allowed.

6)☒ Claim(s) *2,3,6,8-11,13,16,17 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 February 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

The following is responsive to applicant's amendment received March 1, 2004 and letter dated Nov. 15, 2004.

Claims 2, 4-5, 7, 12, 14-15, 18 are cancelled. New claims 20-25 are added. Claims 2-3, 6, 8-11, 13, 16-17, 19-25 are currently pending.

The previous claim rejection under 35 USC 112, first paragraph, set forth in paragraph 1 of the office action mailed Aug. 25, 2003, is withdrawn in view of applicant's amendment and the remarks contained therein.

The claims and specification have been subjected to further review. Accordingly, the following new ground(s) of rejection is respectfully submitted.

New Ground(s) of Rejection

Claim Rejection(s)—35 USC 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 8-11, 13, 16, 17, 19, 2, 3, 6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating Type II diabetes, does not reasonably provide enablement for the treatment of Alzheimer's disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

2. In this regard, the application disclosure and claims have been compared per the factors indicated in the decision *In re Wands*, 8 USPQ2d 1400 (Fed. Cir., 1988) as to undue experimentation. The factors include:

1) the nature of the invention;
2) the breadth of the claims;
3) the predictability or unpredictability of the art;
4) the amount of direction or guidance presented;
5) the presence or absence of working examples;
6) the quantity of experimentation necessary;
7) the state of the prior art; and,
8) the relative skill of those skilled in the art.

The relevant factors are addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

Factors 1 and 2) The claimed inventions are directed to compositions and methods of treating Alzheimer's disease, comprising administering a pharmacological agent containing an effective amount of plant matter from a plant of the genus *Uncaria*, species *tomentosa* in combination with various herbal compounds and vitamins.

Factor 3) There is a known unpredictability in the art when engaging in the treatment of Alzheimer's disease, since it is generally suggested that the incidence of the disease is associated with genetic mutation, especially that which results from familial transmission, but such a correlation between Alzheimer's disease and genetic transmission is not absolutely confirmed (see Cecil's Textbook of Medicine, "Genetics of Alzheimer's Disease", p.2043-2044). Although there are a number of therapies that can be used for the amelioration of symptoms, such as

acetylcholinesterase inhibitors (tacrine and donepezil), vitamin E, or neuroleptic agents (haloperidol, risperidone, olanzapine or quetiapine), the use of any one or more of these therapies is not recognized in the art to guarantee improvement of the symptoms associated with such a disease. Behavioral interventions are also recognized as effective therapies in managing patients with Alzheimer's disease (Cecil's, 'Treatment", p.2044). However, although the etiology of the disease is generally suggested to arise from genetic mutation, genetic screening of asymptomatic patients for early diagnosis has not proven to be of any benefit (Cecil's, "Diagnosis", p.2044). As a result, therapeutic treatments that prevent the advancement of symptoms associated with the condition is not recognized in the art.

Factor 4) Applicant has merely disclosed that by administering the claimed active agents in a patient diagnosed with Alzheimer's disease, one may treat a condition in the patient. Please see page 6. Based on the discussion in Section 3 above, however, such disclosure clearly is not adequate direction or guidance as to how the claimed combinations could be employed to accomplish the complete treatment of Alzheimer's disease in a predictable manner.

Factor 5) The specification at page 6 merely discloses that a patient diagnosed with Alzheimer's disease may take, orally, a composition containing a mixture of plant matter from Uncaria tomentosa, i.e. PTI-00703, and a mixture of Gingko Biloba, ginseng, gotu kola, echinacea, vitamin E, selenium, niacin, folic acid, vitamin B12 and choline.

Additionally, Study 1 assesses the effects of a claimed combination on amyloid fibril formation associated with Alzheimer's disease. Study 2 assesses the effects of a claimed

combination on amyloid fibril growth associated with Alzheimer's disease. Study 3 assesses the effects of a claimed combination on Aβ-glycosaminoglycan interactions associated with Alzheimer's disease. Study 4 assesses dose-dependent effects on causing dissolution or disruption of pre-formed amyloid (1-40) fibrils associated with Alzheimer's disease. Study 5 assesses the dose dependent effects on causing dissolution or disruption of pre-formed amyloid 1-42 fibrils associated with Alzheimer's disease. Please see pages 10-15

Results demonstrate that a claimed combination, i.e. PTI-00703 + Gingko biloba was a potent inhibitor of amyloid fibril formation (study 1), was effective in inhibiting amyloid fibril growth (study 2), was an inhibitor of beta-amyloid protein-PG/GAG interactions (study 3), was effective in causing dissolution or disruption of pre-formed amyloid (1-40) fibrils in a dose-dependent manner (study 4) and was effective in causing dissolution or disruption of pre-formed amyloid (1-42) fibrils in a dose-dependent manner (study 5). Please see pages 15-17. Finally, page 19 of the specification teaches possible syngergism between PTI-00703 and Gingko biloba in inhibiting amyloid fibril growth.

However, in light of the state of the art, which recognizes particular conventional therapies, such as acetylcholinesterase inhibitors (tacrine and donepezil), vitamin E, or neuroleptic agents (haloperidol, risperidone, olanzapine or quetiapine), or behavioral modifications, (See Factor 7, below), effective in ameliorating symptoms of Alzheimer's disease, the Office would require appropriate disclosure to support the contention that the use of the claim specified active agents could actually improve the symptoms or prevent the development or advancement of Alzheimer's disease by simply administering, by any method, an amount of the claimed active agents.

Factor 6) Since the present specification would not enable the skilled artisan to treat Alzheimer's disease, a clear burden of undue experimentation would be placed upon the skilled artisan in order to practice this aspect of the invention.

Factor 7) Conventional therapies used to treat and control the conditions and symptoms associated with Alzheimer's disease, such as acetylcholinesterase inhibitors (tacrine and donepezil), vitamin E, or neuroleptic agents (haloperidol, risperidone, olanzapine or quetiapine), and behavioral modifications (see Cecil's Textbook of Medicine, "Alzheimer's Disease", p.2043-2045) are well known in the art as treatments for ameliorating the symptoms and conditions associated with Alzheimer's disease. However, it is more difficult to treat Alzheimer's disease by improving symptoms or preventing the development or advancement of Alzheimer's disease than it is to simply ameliorate and control the symptoms associated with the condition, since the etiology and pathophysiological manifestations of the disease are not particularly well understood or characterized.

Furthermore, the art acknowledges only certain criteria for definitive diagnosis of Alzheimer's Disease, see in particular Gauthier et al., Can. Med. Assoc. J, Oct 15, 1997, 157(8):1047-52, Greicius et al., J Neurol. Neurosurg. Psychiatry, 2002 Jun; 72(6):691-700 and Gasparini et al., FASEB J., 12, Jan. 1998, pp. 17-34. Post mortem analysis of brain tissue for the characteristics of Amyloid plaques is considered necessary. This is because the art has come to recognize its presence in essentially all cases. However, to achieve diagnostic status took years of evaluative procedures both pre and post mortem confirming that every case has a degree of the

pathology. Even so, diagnostic application is often problematic given variable peptide expression patterns amongst clinically similar and dis-similar disease states, see in particular Greicius.

Factor 8) In view of the discussion of each of the preceding seven factors, the level of skill in this art is high and is at least that of a medical doctor with several years of experience in the art.

As the cited art and discussion of the above 8 factors establish, practicing the claimed method in the manner disclosed by Applicant would not imbue the skilled artisan with a reasonable expectation that treatment of Alzheimer's disease could be achieved. The skilled artisan would be faced with the impermissible burden of undue experimentation in order to practice the claimed invention. Accordingly, claims 8-11, 13, 16, 17, 19, 2, 3, 6 are deemed properly rejected.

Allowable Subject Matter

Claims 20-25 are free from the prior art because the prior art does not disclose or fairly suggest the claimed pharmaceutical compositions.

Conclusion

Claims 8-11, 13, 16, 17, 19, 2, 3, 6 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Cybille Delacroix-Muirheid** whose telephone number is **571-272-0572**. The examiner can normally be reached on Mon-Thurs. from 8:30 to 6:00 as well as every other Friday from 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Christopher Low**, can be reached on **571-272-0951**. The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CDM
Nov. 28, 2005

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